

**510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY TEMPLATE**

A. 510(k) Number:

k050784

B. Purpose for Submission:

Clearance of an Aldosterone Assay for urine. The calibrator, controls, and the serum/plasma sample types were cleared in a previous 510(k) k032188 and not the subject of this review.

C. Measurand:

Aldosterone - Urine

D. Type of Test:

Quantitative, Chemiluminescent competitive binding assay

E. Applicant:

Nichols Institute Diagnostics

F. Proprietary and Established Names:

Nichols Advantage® Aldosterone Assay

G. Regulatory Information:

1. Regulation section:

21 CFR §862.1045, Aldosterone test system

2. Classification:

Class II

3. Product code:

CJM

4. Panel:

75, Chemistry

H. Intended Use:

1. Intended use(s):

See indications for use below.

2. Indication(s) for use:

The Nichols Advantage Aldosterone Assay is intended for in vitro diagnostic laboratory use with the Nichols Advantage® Specialty System for the quantitative measurement of aldosterone in human serum, EDTA plasma and extracted urine. Aldosterone measurements are intended for use in the diagnosis and treatment of primary aldosteronism (a disorder caused by excessive secretion of aldosterone by the adrenal gland), hypertension caused by primary aldosteronism, selective hypoaldosteronism, edematous states and other conditions of electrolyte imbalance.

3. Special conditions for use statement(s):

N/A

4. Special instrument requirements:

Nichols Advantage® Specialty System (k961142)

I. Device Description:

Nichols Institute Diagnostics utilizes chemiluminescence acridinium esters as the label in its specialty chemiluminescence system. Acridinium esters emit light upon treatment with hydrogen peroxide and an alkaline solution. Trigger 1 solution contains hydrogen peroxide in dilute acid and the Trigger 2 solution contains dilute sodium hydroxide. The system automatically injects Trigger 1 and 2 solutions into the well of the cuvette, which oxidize the acridinium ester. The oxidized product is in an excited state. The subsequent return to ground state results in emission of light, which is quantified in two (2) seconds and is expressed in relative light units (RLU) by the integrated system luminometer.

The human source material used in the preparation of this product has been found negative for the presence of the antibody to Human Immunodeficiency Virus (HIV-I and HIV-II), HCV and HBV by FDA approved methods.

J. Substantial Equivalence Information:

1. Predicate device name(s):

DSL-8600 Active® Aldosterone Coated-Tube Radioimmunoassay Kit

2. Predicate 510(k) number(s):

k943397

3. Comparison with predicate:

| Similarities | | |
|---|--|---|
| Item | Device | Predicate |
| Specimen type | Serum, plasma and 24 hour urine | Serum, plasma and 24 hour urine |
| Specific monoclonal antibody (Mab) to aldosterone and assay general principle | Mab utilized within a direct competitive immunoassay method to measure the aldosterone in urine after extraction | Mab utilized within a direct competitive immunoassay method to measure the aldosterone in hydrolyzed urine. |

| Differences | | |
|----------------------------------|---------------------------------|-----------------------------------|
| Item | Device | Predicate |
| Sample Volume | 250 microliters | 100 microliters |
| Analytical sensitivity | 1.2 ng/dL | 0.7 ng/dL |
| Incubation steps and temperature | 180 minutes at room temperature | 3 steps, 10 minutes each at 37° C |

K. Standard/Guidance Document Referenced (if applicable):

FDA Guidance FOD#471 “In Vitro Diagnostic Devices: Guidance for the Preparation of 510(k) Submissions”, January 1, 1997.

FDA Guidance FOD#4444 “Guidance for Industry and FDA Staff – Use of Symbols on Labels and in Labeling of In Vitro Diagnostics Devices Intended for Professional Use”, November 11, 2004

NCCLS Guidance Document EP5-A: Evaluation of Precision Performance of Clinical Chemistry Devices; Approved Guideline. Feb. 1999, Vol. 19, No 2. NCCLA, 940 West Valley Road, Suite 1400, Wayne \, PA 19087-1898 USA.

NCCLA Guidance Document LA1-A2 [1994]: Assessing the Quality of Radioimmunoassay Systems – Second Edition; Approved Guideline. (In Vitro Diagnostics); NCCLS, 940 West Valley Road, Suite 1400, Wayne \, PA 19087-1898 USA.

NCCLS Guidance Document EP5-A: NCCLS I/LA21-A [2002]: Clinical Evaluation of Immuno-assays; Approved Guideline. (In Vitro Diagnostics); NCCLS, 940 West Valley Road, Suite 1400, Wayne \, PA 19087-1898 USA.

L. Test Principle:

The aldosterone assay is based upon competitive binding between aldosterone in the sample and acridinium ester labeled aldosterone (labeled aldosterone) for a specific mouse monoclonal antibody to human aldosterone. First, sample is incubated with biotinylated anti-aldosterone monoclonal antibody for 10 minutes at 37 °C. Next, labeled aldosterone is added to the reaction mixture. In the second incubation, aldosterone from the sample competes with labeled aldosterone for binding to the specific monoclonal antibody. In the third and final 10 minute incubation, streptavidin-coated magnetic particles and assay buffer are added into the reaction mixture. Because of the high affinity between biotin to streptavidin, biotinylated monoclonal antibody rapidly binds to the streptavidin-coated magnetic particles. The captured complex bound to the magnetic particles is then washed by the system to remove unbound components and labeled aldosterone. The cuvette wells containing the washed magnetic particles are moved into the system luminometer, which automatically adds trigger 1 and 2, initiating the chemiluminescence reaction. The light is expressed as relative light units (RLU). The amount of RLU is proportional to the amount of labeled aldosterone bound to the magnetic particles. The RLU signal when read-off the stored calibration curve is inversely proportional to the aldosterone concentration in the sample.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

The within-run and total imprecision for urinary aldosterone extraction method was estimated using the NCCLS EP5-A method. The data represents one run per day over 20 days for each extracted urine pool or assay control run in duplicate. The results are presented in the table below:

| Urine Sample | Mean | Within-Run | | Total Imprecision | |
|--------------|---------|------------|------|-------------------|-------|
| | (ng/dL) | SD | %CV | SD | %CV |
| Sample A | 8.6 | 0.53 | 6.1% | 1.32 | 15.3% |
| Sample B | 17.6 | 0.4 | 2.3% | 1.95 | 11.1% |
| Sample C | 37.4 | 0.61 | 1.6% | 3.84 | 10.3% |
| Sample D | 61.2 | 1.32 | 2.2% | 6.21 | 10.2% |

b. Linearity/assay reportable range:

Parallelism:

Samples with varying concentrations of aldosterone were manually diluted with Urine Diluent and assayed. The data is presented in the table below:

| Sample | Dilution | Observed ng/dL | Expected ng/dL | % Recovery |
|--------|-----------|----------------|----------------|------------|
| 1 | Undiluted | 67.4 | | |
| | 1:2 | 34.3 | 33.7 | 102% |
| | 1:4 | 17.9 | 16.9 | 106% |
| | 1:8 | 7.2 | 8.4 | 85% |
| 2 | Undiluted | 82.2 | | |
| | 1:2 | 41.3 | 41.1 | 100% |
| | 1:4 | 20.5 | 20.5 | 100% |
| | 1:8 | 9.4 | 10.3 | 92% |
| 3 | Undiluted | 92.3 | | |
| | 1:2 | 49.1 | 46.1 | 106% |
| | 1:4 | 24.9 | 23.1 | 108% |
| | 1:8 | 13.3 | 11.5 | 116% |
| 4 | Undiluted | 86.2 | | |
| | 1:2 | 46.4 | 43.1 | 108% |
| | 1:4 | 23.7 | 21.6 | 110% |
| | 1:8 | 11.4 | 10.8 | 106% |
| 5 | Undiluted | 74.7 | | |
| | 1:2 | 40.8 | 37.3 | 109% |
| | 1:4 | 20 | 18.7 | 107% |
| | 1:8 | 9 | 9.3 | 96% |

Recovery:

Three sets of high and a low/normal sample were mixed in 1:2, 1:1 and 2:1 ratios and assayed. The recoveries were determined from the undiluted results. The results demonstrate good recovery (93-110%).

c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*

Controls and calibrators were reviewed and previously cleared k032188 and not reviewed with this submission. However the adjusted master curve stable has gone from 5 days to fourteen days. This was confirmed by testing calibrators, controls and pools over a 30 day period. Acceptance criteria is defined as statistically insignificant slope, average change in dose from Day 0 < 10% and change in the lower or upper 95% confidence interval of the slope < 15%. The controls and pools were within acceptable limits, supporting the claimed stability of 14 days.

d. *Detection limit:*

The analytical sensitivity (Limit of Detection, LOD) was determined by reading the -2SD response from n=20 replicate measurements of the zero standard from the stored master curve from several runs and instruments. The analytical sensitivity for this assay was estimated to be ≤ 1.2 ng/dL.

The functional sensitivity (Limits of Quantification (LOQ)) was determined by detecting the lowest concentration at which an acceptable CV 20% can be obtained. The functional sensitivity for this assay was estimated to be 3 ng/dL

e. *Analytical specificity:*

The anti-sera for the assay are very specific for aldosterone and demonstrates extremely low cross-reactivity to other steroidal compounds in patient samples. Cross-reactivity in the chart below was calculated on a weight-per-weight basis at approximately 50% binding intercept or less.

| Cross-reactant | Cross-reactant conc. Tested (ug/dL) | Apparent Amt. Detected (ng/dL) | % Cross-reactivity |
|---|--|-----------------------------------|--------------------|
| 17-Hydroxy Corticosterone (Cortisol) | 5000 | 23.9 | Undetectable |
| | 2500 | 24.2 | Undetectable |
| | 1250 | 27.5 | Undetectable |
| Cortisone | 45.0 | 26.0 | Undetectable |
| | 22.5 | 25.3 | Undetectable |
| | 11.3 | 25.4 | Undetectable |
| 17-Ketosteroids (DHEA) | 9000 | 21.7 | Undetectable |
| | 4500 | 27.0 | Undetectable |
| | 2250 | 27.0 | Undetectable |
| Estradiol | 9.0 | 26.6 | Undetectable |
| | 4.5 | 27.4 | Undetectable |
| | 2.3 | 28.9 | 0.85% |

| Cross-reactant | Cross-reactant conc. Tested (ug/dL) | Apparent Amt. Detected (ng/dL) | % Cross-reactivity |
|----------------|--|-----------------------------------|--------------------|
| Estrilol | 59.0 | 26.3 | Undetectable |
| | 29.5 | 27.8 | Undetectable |
| | 14.8 | 28.3 | Undetectable |
| Aldosterone | 2.9 | 37.5 | 102% |
| | 1.5 | 44.0 | 98% |

f. Assay cut-off:

Not applicable.

2. Comparison studies:

a. Method comparison with predicate device:

The Nichols Advantage Aldosterone assay was compared to a commercially available aldosterone RIA method. 118 24-hour urine samples were assayed by both methods. The range of values observed with the commercial RIA method was 0.8–80.2 µg/24 hours; and the range of values observed with the Nichols Advantage Aldosterone method was 0.4-66.7 µg/24 hours. Passing Bablok regression analysis yielded an equation of $y=1.23x-1.19$ (95% confidence intervals of the slope and intercept were 1.2-1.28 and -1.43 to -0.81, respectively). Pearson's correlation coefficient of the paired data was $r = 0.96$ (95% confidence interval was 0.94-0.97).

b. Matrix comparison:

Not applicable.

3. Clinical studies:

a. Clinical Sensitivity:

Not applicable.

b. Clinical specificity:

Not applicable.

c. Other clinical supportive data (when a. and b. are not applicable):

Not applicable.

4. Clinical cut-off:

Not applicable

5. Expected values/Reference range:

Twenty-four urine samples were collected from 80 (41 females and 39 males) apparently healthy normal adults 18 to 78 years of age. None of the females were pregnant, taking birth control pills or on estrogen treatment and none were on any medications. After square root transformation of the data, the 95% confidence interval for normal 24-hour urine aldosterone results was as follows: 0.7(0.4 to 1.2) to 23.0 (18.3 to 28.6) µg/24 hours.

N. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

O. Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.